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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,331	10/04/2000	Pierre Deslongchamps	6670/0H748	6557

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/679,331	DESLONGCHAMPS ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 3, 2003 has been entered.

2. Claims 24-33 were pending. Applicant canceled claims 24-33 and added claims 35-37. Please note that claims 35-37 were renumbered in accordance with 37 CFR 1.126, because claim 34 was never entered. Therefore, claims 35-37 are renumbered as claims 34-36. The Examiner respectfully requests that Applicants include with their next Response a copy of all pending claims with the corrections stated above to preserve the clarity of record. An action on the merit follows.

3. Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

4. All previous rejections under the second paragraph of 35 U.S.C. 112 are withdrawn in view of Applicant's amendments and/or cancellation of claims. The "written description" and

"new matter" rejections under 35 U.S.C. § 112, first paragraph are withdrawn in view of Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

5. Claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for several of the tethered tripeptides that are structurally related to the "RGD" compounds (wherein "R" stands for "arginine", "G" stands for glyicine and "D" stands for aspartate) that fall within the broad scope of the claimed invention (see below), is not enabling for the vast majority of compounds that are currently claimed. This is an enablement rejection.

Any person skilled in the art to which it pertains, or with which it is most nearly connected, would not know how to make and **use** the claimed invention. Applicants have not provided enough examples of how to make and **use** the claimed invention to be enabling for the full breadth of the claims. It is clear from applicant's specification how one might practice this invention with the top two compounds in claim 10 (see original claims, page 53 of specification) because they mimic RGD and it is clear from the specification and known in the literature that these compounds might show similar biological activity to known RGD compounds (see specification, page 11, first paragraph, which teaches a known use in the literature for RGD compounds in cell recognition).

However, applicants have not provided sufficient guidance as to how to make and **use** any of the other compounds that fall within the broad scope of the claimed invention, which are not related to RGD.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: Applicant concedes that the breadth of the claims is broad (see specification, page 12, second paragraph) ("the scope of the invention is broad"). Applicant's formula (1) for a macrocyclic compound in claim 1 reads on an almost unlimited number of compounds because of the enormous number of variable groups that can be independently varied (even for the newly added claims). For example, a variable number of amino acids, non-standard amino acids (e.g., β-, γ- amino acids), D and L amino acids (note that changes in stereochemistry would also lead to "structures very different from conventional β-turns"), spacer groups, all containing different R_1, R_2 and R_3 amino acid side chains (20 total) can be independently

varied. Furthermore, different core structures could also be created by using different A1, A2, A3 and T substituents leading to an enormous number of unrelated compounds. (3 and 5) The state of the prior art and the level of predictability in the art: The therapeutic value for the vast majority of these macrocyclic compounds is not known in the literature. In addition, applicant concedes that these compounds would not be structurally related in form and function (see specification, page 12, second paragraph) ("the compounds ... can adopt structures very different from conventional β-turns, according to the nature of their spacer parts") (emphasis added). Thus, it is not possible to determine what effect these substitutions and changes in conformation will have on the therapeutic value (if any) of these macrocyclic compounds i.e., the nature of the subject matter is completely unpredictable (e.g., see Parsons et al, conclusion, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study"; see also specification page 12, paragraph 2, "the compounds according to the invention ...can adopt ***very different structures*** ... ***according to the nature of their spacer parts*** [and, as a result,] ... the ***scope*** of the invention ***is broad***") (emphasis added).

Furthermore, it would be hard to predict what biological target should be used to screen many of these compounds for biological activity and even harder to predict whether or not they would show biological activity (see Parsons et al, conclusion, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a prior* but must be determined from case to case by

painstaking experimental study"). Even if a biological target was known, the structures of the possible variants are sufficiently diverse that one of ordinary skill would not be able to predict which compounds would be capable of binding to the given biological target (see specification page 12, paragraph 2, "the compounds according to the invention ...can adopt ***very different structures*** ... ***according to the nature of their spacer parts*** [and, as a result,] ... the ***scope*** of the invention ***is broad***" demonstrating the unpredictable nature of the claimed invention because it reads on many "unrelated" i.e., very different structures). Therefore, the state of the prior art and the level of predictability in the art is quite low.

(4) The level of one of ordinary skill: The level of skill would be high, a person would most likely hold a Ph.D. level degree.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided any examples for the vast majority of compounds that fall within the scope of these broad claims which show their **usefulness**. Therefore, one of skill in the art would not know how to make and **use** the claimed invention (with the exception of the RGD analogs as mentioned above). Furthermore, there is no generic strategy for determining what effect these substitutions and resulting conformational changes will have on the binding affinity and/or selectivity (note: in paper 11, Applicants make only an unsubstantiated claim that all of the newly amended claimed elements would "limit conformational flexibility" presumably to somehow overcome this rejection). In addition, there is no "core" structure from which a biological entity might bind to (i.e., an "XXX" tripeptide is not an "art recognized" binding motif). Applicants'

claims are not limited to any recognizable core structure (i.e., an RGD tri-peptide, which is an "art recognized" binding motif) and, as a result, there can be no common structural motif to which a biological ligand of interest would bind (i.e., Applicants' claimed XXX structure is not an "art recognized" binding motif). Applicants' claims also encompass non-natural amino acids (e.g., β- and γ-), which add yet another layer of unpredictability to the claimed subject matter.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification for all the reasons asserted above does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and **using** the full scope of the claimed compounds. For example, it is not clear what immediate value a compound of formula (1) would have (referring to claim 34) to the public when the A_1 represents a β- or γ-amino acid with a methyl side chain, the A_2 represents a β-amino acid with an aromatic ether side chain, A_3 represents a D-amino acid with a methionine side chain, and the tether (T) is $-CH_2-S-CH_2-CH_2-$ linker. It would take undue experimentation to determine this value because as applicant concedes the "compounds according to the invention have much flexibility and can adopt structures very different from conventional β-turns, according to the nature of their spacer parts."

Furthermore, applicant concedes that the vast majority of these compounds are only "potentially" useful in a research setting (see specification, page 19, second paragraph) ("Among the potential uses of the compounds according the present invention are uses in scientific research as research reagents") and only provides a long "non-

specific" list of potential diseases where these macrocyclic compounds "might" some day be useful (see pages 18-19 showing a long non-specific list of potential diseases). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and **use** the invention **as broadly as it is claimed**. See also *Brenner v. Manso*n, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Until some actual and specific significance (i.e., biological activity) can be attributed to the vast majority of Applicants' claimed compounds, the instant invention is incomplete. In the absence of knowledge of the natural substrate or biological significance for the vast majority of Applicants' claimed compounds, there is no immediately obvious patentable use for them. Since the majority of the claimed compounds are not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to make and **use** the claimed invention **as broadly as it is claimed**. Therefore, Applicant's claimed invention is not enabled.

Response to Arguments

6. Applicant's arguments directed to the above Enablement rejection were considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' arguments and/or newly amended and/or newly added claims.

[Wands factors 1-2] Applicants argue that they have narrowed their claims such that the specification as filed provides Enablement for the newly added claims (see 11/3/2003 Response, pages 29-30).

[Wands factor 4] Applicants argue "Given the disclosure in the specification regarding the particular compound structures ... a person of ordinary skill in the art would have all of the information needed to make and use the compounds of claims 35 and 35" (see 11/3/2003 Response, page 30, first full paragraph).

[Wands factors 6-7] Applicants argue, "The Examiner acknowledges ... that examples of RGD analogs are provided ... As discussed above, representative examples of tethered tripeptides are provided in the Tables and the text of the specification. These examples cover a representative cross-section of the compounds ... together with the remainder of the specification provide the guidance that would be required to enable one of ordinary skill to make and use the compounds of claims 35 and 36 (see 11/3/2003 Response, page 30, second full paragraph).

This is not found persuasive for the following reasons:

[Wands factors 1-2] the Examiner contends that Applicants newly added claims are still broad and of an unpredictable nature as set forth in Wands factors 1-2 (see above rejection). The newly amended claims would still encompass an almost unlimited number of chemical unrelated compounds. Furthermore, Applicants have not set forth **any evidence** refuting the Examiner's position that Applicants broad scope would also be of "unpredictable" nature (see specification page 12, paragraph 2, "the compounds according to the invention ...can adopt ***very different structures*** ... ***according to the nature of their spacer parts*** [and, as a result,] ... the ***scope*** of the invention ***is broad***"). Furthermore, Applicants have not put forth **any evidence** that would

indicate that their amendments would alleviate this problem other than to make an unsubstantiated claim that "No further information beyond that disclosed in the instant specification would be required by those skilled in the art in order to make and use the compounds called for in claims 35-37 [now renumbered 34-36, see above]" (see 11/3/2003 Response, page 29, paragraph 4). This statement is not afforded ***any*** weight because there is **no data to support this position**.

[Wands factor 3 and 5] Applicants did not refute Wands factors 3 and 5 (see rejection above) and, as a result, the Examiner holds this to be an implicit concession on the part of Applicants.

[Wands factor 4] Applicants' arguments do not address this issue. They seem to confuse the "level of ordinary skill" in the art with the level of "predictability" in the art and/or the amount of "guidance" provided by Applicants. In addition, the Examiner notes that the "level of ordinary skill" has already been determined to be that of a Ph.D. (i.e., the Examiner is conceding this factor).

[Wands factors 6-7] First, the Examiner notes that the rejection above indicates that Applicants are enabled for "tethered tripeptides that are structurally related to RGD" because these compounds have an "art recognized" binding motif. Therefore, the fact that "examples of RGD analogs are provided in the specification" is not relevant to the current enablement rejection because this enablement rejection is NOT drawn to compounds that are structurally related to the RGD tethered tripeptides (i.e., this is a "scope" of enablement rejection).

Second, Applicants statement that their compounds cover a "representative cross-section" of claims 35 and 36 is not germane to the issues set forth by the Examiner in the above rejection

either because it does not address that fact that disclosing the ability to make a compound or a "representative cross-section of said compounds" is in itself insufficient to establish an enabled **use** for said "representative cross-section of said compounds" as determined by the U.S. Supreme Court. e.g., See *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (1966) (see above enablement rejection). The Examiner contends that ONLY the claimed "tethered tripeptides" that are structurally related to the art recognized "RGD tripeptides" are enabled. Please note that the vast majority of Applicants' claimed "tethered tripeptides" are not "structurally related" to the RGD compounds because they do not contain an "R" at the first position, a "G" at the second position and a "D" at the third position as required by the "RGD" motif (i.e., it is not called an "XXX" structural motif where any "X" amino acid can substitute for the essential "R", "G" and "D" amino acids). Consequently, the vast majority of Applicants' claimed compounds are not recognizable as analogous to compounds with a recognized pharmacological activity (i.e., RGD compounds). The Examiner also notes that Applicants have not set forth any **evidence** to contradict this assertion. Therefore, a person of skill in the art would not know what activity to screen for from the large laundry list of potential diseases and/or other biological activities set forth by Applicants. As a result, the Examiner maintains that an undue amount of experimentation would be required i.e., someone else (other than applicant) would have to discover what the vast majority of these claimed compounds would be useful for which clearly represents only an invitation to experiment. See *Brenner v. Manson* cited above.

Accordingly, the rejection cited above is hereby maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Jon D. Epperson, Ph.D.
January 31, 2004

BENNETT CELSA
PRIMARY EXAMINER